Decision Memo for Electrical Bioimpedance for Cardiac Output Monitoring (CAG-00001R2)

Decision Summary

CMS was asked to make a National Coverage Determination (NCD) that would expand Medicare coverage to include Transthoracic Electrical Bioimpedance (TEB) for the management of drug resistant hypertension and additional types of hypertension. Our existing policy permits Medicare contractors to determine whether or not TEB is reasonable and necessary under § 1862(a)(1)(A) for management of drug resistant hypertension. 20.16(A)(2) of the Medicare National Coverage Determination Manual. After considering the additional evidence, we have determined that the evidence does not warrant expanded coverage at this time. Still, we will retain our policy permitting Medicare contractors to make a reasonable and necessary determination under § 1862(a)(1)(A) for the use of TEB in the management of drug resistant hypertension in beneficiaries.

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Decision Memo

TO: Administrative File: CAG #00001R2
Electrical Bioimpedance for Cardiac Output Monitoring

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SUBJECT: Coverage Decision Memorandum for Electrical Bioimpedance for Cardiac Output Monitoring

DATE: November 20, 2006

I. Decision

CMS was asked to make a National Coverage Determination (NCD) that would expand Medicare coverage to include Transthoracic Electrical Bioimpedance (TEB) for the management of drug resistant hypertension and additional types of hypertension. Our existing policy permits Medicare contractors to determine whether or not TEB is reasonable and necessary under § 1862(a)(1)(A) for management of drug resistant hypertension. 20.16(A)(2) of the Medicare National Coverage Determination Manual. After considering the additional evidence, we have determined that the evidence does not warrant expanded coverage at this time. Still, we will retain our policy permitting Medicare contractors to make a reasonable and necessary determination under § 1862(a)(1)(A) for the use of TEB in the management of drug resistant hypertension in beneficiaries.

II. Background

The American Heart Association, in a scientific statement published in its journal *Hypertension,* on January 24, 2006, reported that 27 % of adult Americans have hypertension. Statistics published on the Association's web site indicate that nearly 2/3 of people do not know they have the condition, and that 70% of patients under treatment do not have the condition controlled. The cause is unknown in 90-95% cases of hypertension, although a number of known risk factors may contribute to its development. Cases without specifically recognized causes are referred to as essential hypertension. In the relatively small number of cases in which another discrete disease process, such as renal artery stenosis, is found to cause the elevation of blood pressure, it is then referred to as secondary hypertension. The rationale for treating hypertension, which in and of itself is asymptomatic, is the prevention of end organ damage, e.g. stroke, kidney failure, heart failure, that may develop in patients who have had high blood pressure for many years.

Blood pressure (BP) is reported in millimeters of mercury (mmHg) with two numbers. The first number is the systolic pressure and is a measure of the force of blood propelled through arteries with each contraction of the left ventricle of the heart. The second number is the diastolic pressure and is a measure of the force exerted by blood flow in the arteries between left ventricular contractions. High blood pressure or hypertension is diagnosed by multiple measurements with a medical instrument known as a sphygmomanometer, commonly referred to as a blood pressure cuff. In a given individual, measured blood pressure will vary in response to many factors, including recent physical exertion, fluid status, site of measurement (e.g. left arm, right arm, thigh), the size of the blood pressure cuff, and other factors. Thus, the value of an isolated blood pressure measurement is minimal, and common practice is to base treatment decisions on multiple measurements over time. The measurement should be performed by a qualified health care professional with the patient at rest. Measurements greater than or equal to 140(systolic)/90(diastolic) recorded on multiple occasions are sufficient for the diagnosis of hypertension or high blood pressure. Lower cutoff values have been advocated for some patient populations predisposed to end organ damage, e.g. diabetics.

Treatment of newly diagnosed essential hypertension usually begins with recommendations for lifestyle modification to temper the effects of known risk factors and prevent or delay progression to end organ damage, particularly to the cardiovascular system. Recommended lifestyle changes may include regular exercise, smoking cessation, decreased alcohol intake, sufficient rest, and changes to reduce dietary sodium and fat content as well as to maintain or attain a healthy weight.

If goal blood pressure has not been achieved after a reasonable trial of lifestyle modification, or in the presence of comorbid conditions or predisposing inherited factors, antihypertensive medication is usually prescribed. Usual current recommendations are to begin treatment with a thiazide diuretic (unless contraindicated) and, if goal is still not reached, to add one or two additional medications at therapeutic dose levels until pressure is controlled. Medications have side effects that may be difficult for some patients to tolerate, or the particular drug combination chosen may not sufficiently reduce blood pressure in a particular patient. Physicians may try several drug combinations over a period of time, along with continuance of lifestyle modifications, before achieving long lasting control.

Though there are many individual drugs that may be used for blood pressure control, the actual number of therapeutic options available to treat the patient is somewhat limited. Individual antihypertensive medications typically fall into one of several pharmacologic classes: diuretics, beta adrenergic blockers (β blockers), alpha blockers, calcium channel blockers (CCBs), vasodilators, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs) and centrally acting agents. Within a given class, individual drugs generally lower blood pressure through a common mechanism and display similar side effects. Thus, if a patient fails to respond favorably to a particular drug it is less likely that he will respond favorably to another drug in the same class. With few exceptions, e.g. concurrent use of a potassium sparing and a non-potassium sparing diuretic, patients rarely are prescribed concurrent therapy with multiple drugs belonging to the same class. Generally, the treating practitioner will initiate a new medication at a lower than maximum dose and, if the target blood pressure is not achieved will titrate upwards until the patient experiences intolerable side effects, the maximum labeled dose is reached, or the blood pressure goal is attained.

The proposed role of TEB measurement in the treatment of hypertension is that medication choices based on TEB results may lead to normalization of hemodynamic parameters. In theory, this will in turn result in better BP control. A recent review article listed a number of hemodynamic parameters that TEB is capable of measuring: (Ventura et al, 2005.) These are listed below.

- stroke volume (SV) "the amount of blood ejected from the left ventricle"
- systemic vascular resistance (SVR) "the force the left ventricle must overcome to expel blood into the systemic vasculature, also called total peripheral resistance"
- cardiac output (CO) "the flow of blood pumped by the heart each minute", the product of the heart rate (HR) and SV
- mean arterial pressure (MAP) "the product of two hemodynamic components, CO and SVR"
- thoracic fluid content (TFC), "an index of fluid" with an inverse relationship to total thoracic impedance

In our prior reconsideration decision, two other hemodynamic measures were defined.

- cardiac index (CI), "the CO divided by the patient's body surface area" and
- systemic vascular resistance index (SVRI), which is computed from the CI and stroke volume

III. History of Medicare Coverage

There have been two previous decisions relating to coverage of Electrical Bioimpedance for Cardiac Output Monitoring.

Under the first TEB coverage determination, effective July 1, 1999, TEB was covered for the "noninvasive diagnosis or monitoring of hemodynamics in patients with suspected or known cardiovascular disease." The NCD did not specifically mention use of TEB in connection with treatment of hypertension, nor had evidence for such use been submitted.

On August 7, 2003, CMS issued a reconsideration decision memorandum which clarified the circumstances under which TEB use would be considered reasonable and necessary. Upon review of evidence related to hypertension CMS determined that the coverage and description of the specifics of the situation in which TEB is reasonable and necessary for the treatment of drug resistant hypertension is left to contractor discretion, and that all other uses of TEB for hypertension are noncovered.

Current Request

On February 28, 2006, CMS opened a reconsideration of NCD 20.16 at the request of CardioDynamics. "The purpose of this letter is to formally request that CMS reconsider TEB coverage in hypertension and issue an NCD with the following language: *"TEB is covered for the management of hypertensive patients on one or more antihypertensive drugs who are not at goal blood pressure. TEB is covered for hypertension that is essential or secondary, benign or malignant, or with or without comorbidities."*

By letter on September 23, 2006, the requestor sought to revise its request to:

"*TEB is covered for the following subgroup of patients with hypertension:*

1. Hypertensive patients who are not at goal BP on three or more antihypertensive drugs.
2. High-risk hypertensive patients who are not at goal BP on two or more antihypertensive drugs. High-risk patients are defined by JNC guidelines and include patients with: a. Diabetes mellitus; b. Chronic kidney disease, defined as GFR <60 ml/min or albuminuria (>300 mg/d or 200 mg albumin per gram of creatinine).

Conditions
Prior to receiving a TEB test for hypertension, the patient must have been diagnosed and treated for hypertension a period of at least six months.

Frequency Limitation
TEB testing for hypertension as a covered indication is limited to a maximum of four tests per patient in a 12 month period. If a patient has received a previous TEB test for hypertension, an additional TEB test for hypertension cannot be performed for at least 30 days.

Noncoverage
TEB for hypertension is not covered: a) as a screening test; b) for any patient already at goal BP; c) for any patient not at goal BP on only one antihypertensive drug."

These requests are for expansion of coverage under the current benefit category,

Benefit Category

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage. § 1812 (Scope of Part A); § 1832 (Scope of Part B) § 1861(s) (Definition of Medical and Other Health Services). At a minimum, TEB is considered to be within the benefit category of Diagnostic Tests (other). §1861(s)(3) This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

February 28, 2006	CMS accepts a formal request for reconsideration of TEB for expanded coverage for hypertension. A tracking sheet was posted on the web site and the initial 30 day public comment period commenced.
March 30, 2006	The initial 30 day public comment period ended.
April 6, 2006	Public comments posted to the web site.
August 24, 2006	The proposed decision memorandum inviting public comments was posted. The 30 day public comment period began.
September 23, 2006	The second 30 day public comment period ended.
September 23, 2006	Revised coverage request received.

V. FDA Status

Companies manufacturing TEB devices have obtained clearance for marketing of these devices under the Food and Drug Administration's (FDA) 510(k) process. The FDA considers TEB devices to be Class II devices. The predicate devices upon which clearance was based are previous cardiac output monitors employing impedance plethysmography. Several TEB devices have been cleared through the FDA for marketing to monitor hemodynamic parameters.

VI. General Methodological Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination

VII. Evidence

A. Introduction

We are providing a summary of the evidence that we considered during our review. We considered additional evidence submitted during the two public comment periods.

A reasonable and necessary diagnostic test must provide information that is used by the treating physician to appropriately guide the management of the patient's specific medical problem. 42 CFR. § 410.32(a) A principal outcome of interest in assessing the utility of a diagnostic test is its ability to improve health outcomes of persons who are tested.

B. Discussion of evidence reviewed

1. Question:

Is the evidence sufficient to conclude that hemodynamic monitoring with thoracic electric bioimpedance (TEB), when used by the treating physician to guide management of the patient's medical problem, improves health outcomes in Medicare beneficiaries with hypertension who are on one or more antihypertensive drugs and who are not at goal blood pressure?

2. External technology assessments

CMS did not commission a new external technology assessment (TA) for the current reconsideration request; however, the Agency for Healthcare Research and Quality (AHRQ) did complete a TA on TEB under contract from CMS in 2002. That assessment may be found on the CMS website at http://www.cms.hhs.gov/mcd/viewtechassess.asp?id=23. CMS was unable to locate any other TAs for TEB.

3. Internal technology assessments

CMS performed an extensive literature search utilizing PubMed for new randomized controlled trials (RCTs) and systematic reviews evaluating the use of TEB in the medical management of hypertensive patients. The literature search was limited to the English language and specific to the human population. The CONTROL study provides the only new peer-reviewed published RCT data on the use of TEB in the management of ambulatory hypertensive patients since our previous TEB reconsideration. The terms ICG (impedance cardiography) and TEB are used interchangeably in documents.

The current request for coverage of TEB in the management of hypertension included ten documents, most prominent of which was the recently published "Consideration of Noninvasive Hemodynamic Monitoring to Target Reduction of Blood Pressure Levels" (CONTROL) study (Smith et al, 2006). This publication was accompanied by a published editorial comment and will be presented in greater detail below.

The requestor also submitted a manuscript describing a cost effectiveness analysis of TEB. CMS does not consider cost in making NCDs. This policy is explicitly noted in a guidance document that is publicly available at the URL below.

http://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=6

"Cost effectiveness is not a factor CMS considers in making NCDs. In other words, the cost of a particular technology is not relevant in the determination of whether the technology improves health outcomes or should be covered for the Medicare population through an NCD."

Other documents submitted by the requestor are listed below. Full citations are provided in the References section.

Sramek BB, Tichy JA, Hojerova M, Cervenka V, 1996: Normohemodynamic Goal-Oriented Antihypertensive Therapy Improves The Outcome (abstract only)

This abstract was submitted in support of the last TEB reconsideration request, however no published, peer-reviewed, study is available and therefore it was not used in our analysis.

Sharman DL, Gomes CP, Rutherford JP. 2004: Improvement in Blood Pressure Control With Impedance Cardiography-Guided Pharmacologic Decision Making

This study reports on "impedance cardiography" or ICG (another term for TEB) use in the treatment of 21 older patients whose blood pressure was uncontrolled on two medications. There was no control group. All patients received the same number of visits and ICG measurements and were treated according to the algorithm reported in *Hypertension* which was extensively reviewed in the last CMS reconsideration decision. (Taler SJ, Textor SC, Augustine JE, 2002)

Overall, participants' entry systolic blood pressure (SBP) was 157.2 ± 13.9 and diastolic blood pressure (DBP) was 78.7 ± 9.9. At the end of three months SBP was 147 ± 18 and DBP was 76 ± 11. Subgroup analysis showed that twelve patients (57.1%) achieved blood pressure <140/90, (SBP 126.6 ± 7.8, DBP 73.9 ± 9.7) while nine (42.9%) had final blood pressure >140/90, (SBP 160.7 ± 81.3, DBP 81.3 ± 11.1).

The authors state that the difference in results between subgroups is that patients achieving better control reduced their systemic vascular resistance index (SVRI, measured as dyne x sec x m^2 x cm^5) to a greater extent though use of ICG measurements. ($p<0.05$)

	Entry SVRI	**Final SVRI**
Lower BP group	2986 ± 806	2640 ± 697
Higher BP group	2923 ± 645	3076 ± 468

The authors conclude that patients who were unresponsive to treatment "have an obvious need for further dose or drug changes" such as "intensification of a diuretic regimen" as was done in the 2002 Taler study. However, "(d)iuretics were not widely prescribed in this group…due to patient and physician preference with an appreciation of increased symptoms, and patient noncompliance…often associated with diuretics." It is not clear how problems of physician and patient preference and non-compliance are improved through ICG or TEB, and authors conclude that "(a)dditional reports will continue to refine the role of ICG in the treatment of hypertension."

Sanford T, Treister N, Peters C, 2005: Use of Noninvasive Hemodynamics in Hypertension Management (report of three cases).

The authors report improved blood pressure control in three patients, four to six weeks after medication changes suggested by ICG data. They conclude "individualized approach to therapy may lead to fewer side effects from medications and reduce the number of visits required to achieve BP control." The small number of patients and short follow-up are insufficient to provide information useful to the current decision.

Ashida T, Nishioeda Y, Kimura G, Kojima S, Kawamura M, Imanishi M et al. 1989: Effects of Salt, Prostaglandin, and Captopril on Vascular Responsiveness in Essential Hypertension.

This article provides a brief discussion of mechanisms of hypertension and does not include discussion of the use of TEB.

Alfie J, Waisman GD, Galarza CR, Magi MI, Vasvari F, Mayorga M et al., 1995: Relationship Between Systemic Hemodynamics and Ambulatory Blood Pressure Level are Sex Dependent

This study compares sex-related differences in hypertensive men and women using impedance cardiography to estimate hemodynamic measures and ambulatory monitoring to record blood pressure. The authors concluded that the relationship of "hypertension severity and systemic vascular resistance was dependent on the sex of the patient." This was not a treatment study and did not provide information as to how the results should be used in management of hypertension.

Galarza CR, Alfie J, Waisman GD, Mayorga LM, Camera LA, del Rio M et al.1996: Diastolic Pressure Underestimates Age-Related Hemodynamic Impairment

The authors compared demographic and hemodynamic data (obtained with ICG) to "demonstrate simultaneous age-related impairment in vascular resistance and arterial compliance," which suggest that SBP, but not DBP, is a reliable indicator of hemodynamic abnormalities (high resistance and low arterial compliance) in the elderly. The goal of the study was explanation of mechanisms, not treatment, and it did not show how this information should be used to establish improved blood pressure control.

Hinderliter AL, Blumenthal JA, Waugh R, Chilukuri M, Sherwood A, 2004: Ethnic Differences in Left Ventricular Structure: Relations to Hemodynamics and Diurnal Blood Pressure Variation

One hundred seventy-one men and women, aged 25 to 45 years, equally divided between those with "normal" BP (<140/85 mmHg) and those with "marginally elevated" BP (140-160/85-95 mmHg) received various measurements including ICG, office and ambulatory BP, echocardiograms, Doppler studies and various blood chemistries, which showed "greater left ventricular relative wall thickness in African American subjects as compared to whites with similar levels of resting BP." The authors believe this difference "may be mediated, in part, by hemodynamic influences" and that "enhanced understanding of the genetic and environmental factors that determine these differences in left ventricular load may result in interventions that could lessen the burden of hypertensive heart disease in African Americans." Goal of study was not blood pressure treatment, but rather to explain the reasons for differences in left ventricular structure observed in young African American hypertensives. The study did not show how this information could be used to improve blood pressure control.

Hinderliter AL, Sherwood A, Blumenthal JA, Light KC, Girdler SS, McFetridge J et al., 2002: Changes in Hemodynamics and Left Ventricular Structure After Menopause

Sixty-four premenopausal and 54 postmenopausal women, aged 47 to 55 years with screening BP <180/90 mmHg were studied. They underwent various measurements including ICG, office and ambulatory BP, echocardiograms, Doppler studies, and various blood chemistries. The authors note "that menopause is associated with concentric remodeling of the left ventricle… characteristically seen in subjects with increased peripheral resistance and…associated with and enhanced risk of cardiovascular events." And, "(d)espite nearly identical blood pressures at rest, post menopausal women had a significantly higher peripheral vascular resistance than premenopausal subjects."

The study confirmed earlier investigations, which showed echocardiographic and hemodynamic changes associated with menopause. The study did not suggest how this information could be used to improve blood pressure control.

CMS also noted reference to nine articles in the February 2005 Supplement to the American Journal of Hypertension. One of those articles (Sanford T, Treister N, Peters C, 2005) was submitted with the reconsideration request and is discussed above. We reviewed the other eight articles, but none involved a clinical study using TEB to manage hypertension. Overall, they suggested areas for additional study, but did not provide evidence on health outcomes related to the use of TEB in the Medicare population for the current reconsideration.

A review article (Ventura HO, Taler SJ, Strobeck JE, 2005) concluded that "future studies will confirm recent findings that hemodynamic measurements in individual patients will improve diagnosis, risk assessment and treatment for these patients. It is also possible that further exploration of the implications of hypertension as a hemodynamic disease will lead to studies demonstrating that earlier detection and treatment of the hemodynamic components of hypertension may change the natural history of this disease process."

Another article (Abdelhammed AI, Smith RD, Levy P, Smits GJ, Ferrario CM, 2005), found differences in "hemodynamic profiles between hypertensive and nonhypertensive subjects"…which "may be helpful in diagnostic, prognostic and therapeutic decision making in hypertensive subjects." The article concluded that "significant variation in hemodynamic values among BP categories exists. Hemodynamic findings in an individual patient cannot be predicted by BP values, demographic information, or medications. Noninvasive ICG can help to characterize hemodynamic values and to identify variance at similar BP levels, which may improve BP management." These articles have been listed in the bibliography for reader reference.

Summary of the CONTROL trial

No new evidence was submitted with the revised coverage request dated September 23, 2006; however, the document contained responses to issues raised in our draft decision memorandum, which will be discussed below.

The stated hypothesis of the CONTROL trial was that "ICG-guided treatment could aid physicians in reducing BP more effectively than standard care in a population of uncontrolled hypertensive patients receiving 1 to 3 medications in a primary care setting."

Between November 2002 and November 2004, eleven primary care centers screened 262 patients with a diagnosis of essential hypertension, aged 18 to 75, on 1 to 3 antihypertensive medications with systolic BP140-179 mmHg and/or diastolic BP 90-109 mmHg. Exclusion criteria were:

- >3 antihypertensive medications,
- history of heart failure,
- ejection fraction (EF) <40%,
- atrial fibrillation,
- severe valvular or renal disease,
- nephrotic syndrome,
- cirrhosis, and
- a cerebrovascular event within 3 months.

Patients were also excluded if they had "abnormal laboratory findings" that are not further described, nor were any laboratory values reported in the study. By letter the requestor has advised that these lab values were:

- Hematology: hemoglobin <10g/dL; WBC <2000/mL; platelets <100,000/mL
- Blood chemistries: ALT and/or AST >2.5x upper limit of normal; creatinine >3.0mg/dL; potassium <3.3mEq/dL; Hemoglobin A1c > 10%

Technical limitations of ICG also caused exclusion for height <47 or >75 inches, weight <66 or >341 pounds, hypersensitivity to sensor gel or adhesive, skin lesion at a sensor site, or the presence of activated minute-ventilation pacemaker.

One-hundred eighty-four patients were randomized in a 3:2 ratio to either standard care or ICG-guided care. After randomization, 18 patients were excluded for BP < 140/90 upon remeasurement, and 2 patients withdrew early from the study. No information was provided about the method of randomization in the published report of the trial. The requestor subsequently advised CMS that all trial participants remained under the treatment of their usual physicians. By letter we were advised that "Randomization was stratified by site with block randomization through a central telephone service". The duration of the selection process and how the actual selections were made has not been provided and we have not determined what other efforts may have been employed to reduce bias.

The authors did not indicate the number of patients lost in each study arm, but subsequently, by letter, we were advised that "18 patients (11 standard, 7 hemodynamic) who had systolic BP <140 mm Hg and diastolic BP <90 mm Hg at screening" were excluded because post-washout BP (which was higher) rather than screening BP had been used for selection. Two patients moved and were not further evaluated. The other 18 patients completed an average of 3.4 visits during the study. A chart indicated that if these patients were included in final analysis the 77 patients in the HC arm would have had an SBP change of -17±18 compared to -9±4 for the 105 patients in the standard arm. We have confirmed with the requestor that there was a transposition in the data presented in the letter regarding DBP change and that the correct information for the hemodynamic arm was -10±11 and -4±12 in the standard arm. Mean screening SBP for the 8 patients eliminated from the hemodynamic arm was 131 and mean DBP was 70. In the standard care arm for the 12 patients eliminated mean SBP was 126 and DBP 73.

The trial was not an intention-to-treat analysis and data for these 20 patients were excluded from the published report of the trial. Authors offered no explanation for the 3:2 ratio of patients in the standard care group versus the ICG group, but the requestor advises by letter that: "(t)he larger number of patients in the standard arm of CONTROL was … done to increase the confidence that the standard arm results would reflect primary care results and would not be due to chance. This meant that significantly more patients were enrolled than would have been required for a trial with a 1:1 ratio".

Each of the 164 analyzable patients in the study had a total of five study visits at which BP and ICG measurements were made. Following a baseline visit they underwent a two week washout period during which all antihypertensive medications were discontinued. They received a post-washout visit at which physicians "prescribed medications consistent with published guidelines, their usual practice patterns, and patient clinical characteristics." This was followed by three monthly visits at which BP was measured and ICG data were obtained on all patients, "but ICG findings were not revealed in the standard arm to treating physicians or patients."

In the hemodynamic arm, physicians were encouraged to use but not required to follow a hemodynamic treatment strategy (a simplified and somewhat modified version of the treatment algorithm proposed by Taler et al. (Taler SJ, Textor SC, Augustine JE, 2002). That "Hemodynamic Treatment Algorithm" is included in CMS' August 3, 2003 "Decision Memorandum for Electrical Bioimpedance for Cardiac Output Monitoring." No explanation for differences between the two treatment guides was offered in the published trial description. By letter, the requestor states: "The suggested medication choices based on hemodynamic data were very similar to the Mayo Clinic (Taler) algorithm except for the use of thoracic fluid content (TFC) with diuretics. Because diuretics are suggested first-line therapy in JNC guidelines, we did not want to suggest that TFC needed to be used to determine whether diuretics should be initiated. So, instead, the CONTROL hemodynamic treatment strategy suggested using visit-to-visit TFC changes as indicator of diuretic effectiveness. This is in contrast to the Mayo Clinic's use of TFC as absolute indicator for intensification of diuretics. Since most of the patients in the Mayo Clinic trial were already on diuretics at baseline, it represented a different clinical scenario than the patients in CONTROL, many of whom were not on diuretics at baseline."

Data are not provided on adherence to the strategy or differences in outcomes within the hemodynamic group based upon adherence.

The CONTROL study's proposed treatment strategy for the experimental group, employing specific types of drugs to be prescribed based on hemodynamic data, is summarized in the table below.

Hemodynamic Data	Medication Choice*
High Systemic Vascular Resistance Index	Increase dose or add: ACEI, ARB, CCB, VD
Low/Normal Cardiac Index	Consider reduced dose BB
Evaluate visit-to-visit Thoracic Fluid Content	If diuretic previously added/increased and visit-to-visit Thoracic Fluid Content not reduced, consider increase/change: diuretic
High Cardiac Index	Increase dose or add: BB, CAA
Normal Systemic Vascular Resistance Index	Consider reduced dose: VD

Hemodynamic Data	Medication Choice*
Evaluate visit-to-visit Thoracic Fluid Content	If diuretic previously added/increased and Visit-to-visit Thoracic Fluid Content not reduced, consider increase/change: diuretic

* ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CCB: calcium channel blocker; VD: vasodilator; BB: β blocker; CAA: central acting agent.

Patients in both arms were educated about medication compliance and received a follow-up phone call from a nurse between visits. ICG data were discussed with the patient by the treating physician in the hemodynamic arm only. Patients were asked how many of their prescribed pills they had taken at each visit as an estimate of compliance. The authors report very high compliance overall, including 100% of pills taken in both arms of the trial at the 5th visit. Pill count audits were not done.

The study reports baseline characteristics for patients showing insignificant differences between groups, but some individual items are of interest for a Medicare decision. The mean age of participants is ~ 55 years, about a decade younger than the standard age of Medicare eligibility. Only 4% of the subjects had diabetes, whereas over 20% of adults 60 years and older have diabetes and the prevalence increases with advancing age. Presence of diabetes may affect both the intensity of treatment and the choice of medications in treating hypertension. No information is presented about non-pharmacologic lifestyle modifications that patients may have been prescribed to reduce BP, such as exercise, weight loss, smoking cessation, and decreased alcohol consumption, among others. Such modifications are considered first line therapy in beginning the treatment of hypertension, and generally only when they are unsuccessful are medications begun.

Information is not provided about how long a patient had been under treatment for hypertension prior to study entry. A large percentage of both groups (42% of standard care group and 45% of hemodynamic care group) were on only one antihypertensive medication at baseline. Most guidelines on the treatment of hypertension suggest beginning drug treatment with a single medication (usually a diuretic) and adding additional medications, depending on patient characteristics and presence of comorbid conditions, until control is achieved. The number of patients (18/184 or 10%) excluded from the study after screening when it was found that their BP was <140/90 on repeat examination and the ~43% of study participants on only one medication would seem to indicate either very recently diagnosed disease or lack of intensive effort to control.

At baseline, standard care (SC) patients' BP (in mmHg.) was 147±9/87±10 and hemodynamic care (HC) patients' BP was 148 ±12/89 ±8. After washout, SC BP was 156±13/92±9 and HC was 155±13/94±9. There were no statistically significant differences reported in any hemodynamic measures between the groups at baseline or after washout.

The following table from the CONTROL study summarizes the major findings:

Final BP and Hemodynamic Values

Variable	Standard Care (n=95)	Hemodynamic Care (n=69)	P Value
Systolic BP, mmHg Final Δ baseline to final Δ post-washout to final	136 ± 15 -11 ± 18 -19 ± 17	129 ± 14 -19 ± 17 -25 ± 18	<0.01 <0.01 <0.05
Diastolic BP, mmHg Final Δ baseline to final Δ post-washout to final	82 ± 10 -5 ± 12 -10 ± 11	76 ± 11 -12 ± 11 -17 ± 12	<0.01 <0.001 <0.001
Heart rate, bpm Final Δ baseline to final Δ post-washout to final	77 ± 13 1 ± 12 -2 ± 13	76 ± 11 2 ± 13 -2 ± 13	ns ns ns
Cardiac index, L/min/m² Final Δ baseline to final Δ post-washout to final	2.9 ± 0.5 0.1 ± 0.5 0.0 ± 0.5	2.9 ± 0.5 0.0 ± 0.5 0.0 ± 0.5	ns ns ns
Systemic vascular resistance index, dyne x s x m²/cm² Final Δ baseline to final Δ post-washout to final	2714 ± 619 -219 ± 667 -369 ± 642	2523 ± 581 -433 ± 660 599 ± 738	<0.05 <0.05 <0.05
Thoracic fluid content, /kOhm Final Δ baseline to final Δ post-washout to final	27.8 ± 4.1 -0.8 ± 3.6 -1.2 ± 3.3	28.2 ± 4.9 0.1 ± 3.0 -0.2 ± 2.7	ns ns <0.05

The authors reported generalized information as to how hemodynamic data was used. Specific information as to how a particular hemodynamic measurement was used to change patient treatment was not provided. For example, "In the hemodynamic arm, the initial selection of antihypertensive medications appears to have been influenced by the hemodynamic data, because these patients were more likely to be prescribed a vasodilating agent to reduce SVRI" and "the hemodynamic treatment strategy influenced medication use when SVRI was considered high, because patients in the hemodynamic arm were more likely to have received an ACEI, ARB, or CCB, as was suggested."

The authors state "(i)n theory, the larger drop in SVRI and BP levels in the hemodynamic arm could have occurred through use of more medications, more effective medications, greater dosing intensity, more effective combination therapy, or better patient compliance. Our study allowed full discretion by the physician in choosing the agents, and a multitude of classes and doses within classes were used." They further state the study "was designed to determine whether providing hemodynamic data to the physician and the patient could more effectively reduce BP. Whether hemodynamic data led to a more tailored approach to selection and monitoring of antihypertensive agents or by other factors, it resulted in greater reduction in BP and SVRI and better BP control,"

Publication of the results of the CONTROL study in the April 2006 issue of *Hypertension* was accompanied by an editorial comment, "Noninvasive hemodynamic measurements an important advance in individualizing drug therapies for hypertensive patients." (Flack JM, 2006) While the editorial finds the results of the study "encouraging" it points out that "practitioners did not follow the suggested treatment algorithm to add or increase diuretics when thoracic fluid content did not decrease in response to diuretic initiation or dose escalation" and "did not comply with all the suggested therapeutic decisions in the study treatment algorithm."

Flack lists a number of questions still to be answered relating to IC use in the management of hypertension:

- Does use of IC lead to more rapid control of BP through better pharmacologic choices?
- Does continued use of IC lead to prolonged BP control?
- How should multiple hemodynamic abnormalities be treated?
- Should hemodynamic abnormalities be treated even after normal BP is achieved?
- How quickly would IC be accepted?

MCAC

A Medicare Coverage Advisory Committee (MCAC) meeting was not convened on this issue.

5. Evidence-based guidelines

CMS has not located any evidence-based guidelines for the use of TEB in the treatment of hypertension.

6. Professional Society Position Statements

The American College of Cardiology (ACC) submitted a position statement during the first public comment period that is excerpted below. The entire letter may be viewed in Appendix B and at http://www.cms.hhs.gov/determinationprocess/downloads/id179a.pdf [PDF, 169KB]

"Members of the ACC's Heart Failure and Transplant Committee and Prevention Committee have reviewed the reconsideration request, along with the evidence submitted concerning use of thoracic electrical bioimpedance (TEB) in the management of patients with hypertension. We found that the evidence does not support establishment of national Medicare coverage as requested for hypertensive patients on one or more anti-hypertensive drugs who are not at goal blood pressure. Our clinical experts noted that the two small randomized studies cited by the requester focused only patients with blood pressure that was quite difficult to control. The patients were typically on multiple anti-hypertensive drugs and were, on average obese. These factors limit the extent to which the results of the studies can be generalized to the broader population of patients who have failed to achieve desired blood pressure control on only one or more antihypertensive drugs.

The studies cited do provide some evidence of benefit for a more narrowly defined patient population. The ACC believes that Medicare coverage for patients with drug resistant hypertension, defined as failure to achieve goal blood pressure when adhering to full doses of an appropriate three drug regimen, including a diuretic may be appropriate. We note that the current NCD already provides local Medicare carriers with the explicit discretion to coverage TEB for this patient population".

The ACC submitted a second position statement during the second public comment period supporting their previous position, excerpt below.

"We had previously found that the evidence offered for the first reconsideration was not sufficient to support establishment of national Medicare coverage as requested for hypertensive patients on one or more anti-hypertensive drugs who are not at goal blood pressure. At this time, the ACC has not been presented with sufficient evidence to alter this opinion as expressed in our previous comments on this NCA. We therefore support CMS' proposed decision memorandum as written".

An additional position statement was received in the second public comment period from the International Society on Hypertension in Blacks (ISHIB) opposing our decision to maintain current TEB coverage and requesting extended coverage for TEB:

"We therefore take the position that extending coverage nationally for impedance cardiography will ultimately lead to better patient care and fewer costly pressure related clinical outcomes because of improved therapeutic decision-making and, we posit, less therapeutic inertia. Thus, we support extending coverage for impedance cardiography to high-risk (diabetes mellitus and/or chronic kidney disease according to JNC 7 definitions) on at least 2 antihypertensive medications and to all other hypertensive patients taking at least three antihypertensive drugs".

Both of the above position statements received during the second comment period may be viewed in their entirety in Appendix B and at: http://www.cms.hhs.gov/determinationprocess/downloads/id179b.pdf[PDF, 1MB].

7. Expert Opinion

We have not currently received any expert opinions on the use of TEB for managing hypertension.

8. Public Comments

Initial Comment Period: February 28, 2006 – March 30, 2006

CMS received 217 comments during the 30 day initial public comment period. Three commenters sent the same comment two times – accordingly, 214 comments were actually received. One comment received from the American College of Cardiology is discussed above in the Professional Society Position Statement section.

One hundred eighty-eight comments (88%) were from physicians; 15 (7%) were from nurses, pharmacists, nurse practitioners, and physician assistants; and two commenters (1%) were family members. Nine commenters did not specify their relationship to the issue. No comments were received from persons identified as patients. Most of the public comments were personal experiences submitted by physicians using TEB in their office settings. Two hundred nine (98%) of these comments supported coverage of TEB for the assessment of hypertension in the outpatient setting. Four commenters opposed coverage of TEB and one commenter did not express an opinion. One commenter said that the existing CMS coverage is too expansive. No new published scientific evidence was submitted.

Second Comment Period: August 24, 2006 – September 23, 2006

CMS received 254 comments during the 30 day second public comment period in response to our proposed decision memorandum. Two comments received from professional societies (American College of Cardiology and International Society on Hypertension in Blacks) are discussed above in the Professional Society Position Statement section. None of the other comments included additional medical literature for review.

Two hundred twenty-eight comments (90%) were from physicians and other health practitioners; 22 (9%) were from Medicare patients, one comment each was received from a manufacturer of another cardiac device and a manufacturer's trade association. Eleven of the physicians indicated they were representing group medical practices.

The requestor's revised coverage request was submitted in the form of a public comment and while it sought to add to and clarify data included in the published report of the CONTROL trial, it did not introduce new literature for review. Our response to these materials is incorporated into our revised discussion of the CONTROL trial.

Comment on clinical use of TEB:

Other than the American College of Cardiology comments described above, commenters opposed the proposed coverage decision. As during the previous public comment period, nearly all of the public comments were personal experiences submitted by physicians and others using TEB in their office settings. Many commenters suggested expanding TEB coverage by reducing the number of anti-hypertensive drugs required to obtain coverage. Nine commenters suggested coverage of TEB for patients on one antihypertensive medication, 125 suggested coverage for users of two or more drugs, five suggested three or more drugs, and 115 either expressed no opinion or were unclear in their suggested coverage.

Response:
In reviewing public comments we could find no consensus among medical professionals using the device as to when TEB was medically necessary or how often it needed to be repeated. None suggested either the quarterly schedule and yearly four test limitation or thirty day interval between tests suggested in the requestor's recent letter. Nor did anyone suggest a 6 month attempt at BP control before using TEB. Some physicians appeared to use the device on every hypertensive patient, while others made the point that they used clinical judgment to determine when it could be useful. Frequency of use ranged from rarely on a purely clinical basis depending on experience with a particular patient to as often as 3 to 5 week intervals for up to 6 months, while adjusting medications to achieve goal BP. Not only did comments fail to support the Conditions and Frequency Limitation offered by the requestor in its September 23 revised request, but the nine comments supporting use when on one drug could be considered to be in opposition to the proposal.

Comment on local Medicare contractor discretion:
150 commenters (59%) oppose the current policy of local contractor discretion for coverage of the use of TEB for drug resistant hypertension, mainly because some local Medicare contractors have chosen not to provide coverage.

Response:
Medicare contractors have statutory authority to develop local policy for their jurisdictions. Variation from jurisdiction to jurisdiction is clearly anticipated by and supported by statute.

Comment on CMS' interpretation of the evidence:
Several comments questioned CMS' interpretations of the Mayo Clinic and CONTROL trials. Some stated that the two trials showed improvements in BP control with TEB use and if the results are summed could be considered clinically impressive.

Response:
The Mayo Clinic trial was reviewed in a past reconsideration of this NCD and our detailed analysis of that trial may be found in the decision memorandum that accompanied that reconsideration. Our analysis of CONTROL is included in this decision memorandum.

Comment on patient compliance:
Several commentors made the point that having a printout of the TEB test results encouraged patient compliance with prescribed drugs and that when the test was repeated on subsequent visits patients had visual proof of the efficacy of their efforts to control BP.

Response:
We recognize that physicians may share test results with patients, whether they are derived from TEB, clinical laboratory, radiography or other modalities, in an attempt to motivate patients to comply more fully with recommended treatments. In the case of hypertension, the blood pressure measurement itself is a test result that is routinely shared with the patient at every visit. On October 17, 2006 we conducted an Ovid MEDLINE search using the following terms: Compliance/ or Patient Compliance/ limit 1 to (humans and English language) AND Pharmaceutical Preparations/ad [Administration & Dosage]. We did not find published research on whether compliance, when systematically accessed, is actually improved by the sharing of test results. That absence does not refute the possibility, it simply points to the current lack of evidence to support the anecdotal observations.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." §1862(a) (1) (A). This section presents the agency's evaluation of the evidence considered and conclusions reached for the assessment question.

Question

Is the evidence sufficient to conclude that hemodynamic monitoring with thoracic electric bioimpedance (TEB), when used by the treating physician to guide management of the patient's medical problem, improves health outcomes in Medicare beneficiaries with hypertension who are on one or more antihypertensive drugs and who are not at goal blood pressure?

As a diagnostic test, hemodynamic monitoring would not be expected to directly change health outcomes. Rather, a diagnostic test affects health outcomes through changes in disease management brought about by physician actions taken in response to test results. Such actions may include decisions to treat or withhold treatment, to choose one treatment modality over another, or to choose a different dose or duration of the same treatment. To some extent the usefulness of a test result is constrained by the available treatment options. As noted in the Background section, the number of practical drug treatment options for hypertension is limited by the small number of relevant pharmacologic classes. A patient whose blood pressure is not readily controlled with a tolerated dose of a single drug is likely to be prescribed alternative or additional drug treatment from one or more additional classes. In addressing the question above, one of the factors we consider is whether there is sufficient evidence that the incremental information derived from hemodynamic monitoring leads to improved control of blood pressure by causing physicians to prescribe a different class or dose of antihypertensive medication than they would have prescribed without access to TEB test results.

The choice of specific drugs is influenced by many factors other than their predicted ability, based on class, to reduce blood pressure. Patients who have difficulty accessing a restroom may prefer to avoid a diuretic that causes frequent urination. Other patients may have comorbid conditions such as diabetes or peripheral vascular disease that will influence the use or avoidance of certain drugs. Still other patients may experience adverse events such as edema, erectile dysfunction, or difficulty breathing with particular medications. These other factors may be apparent before the use of a drug, early in the use of a drug, or later after the patient had been on the drug for some time. In summary, the practical pharmacologic treatment options are considerably narrower than the number of antihypertensive drugs, and the true long term suitability of a chosen drug may not be apparent after short term use. A patient might, entirely because of other factors, take the same drug regimen that would have been indicated by TEB results if available. Similarly, a patient might be unable or unwilling over the long term to continue a drug regimen indicated by TEB results.

Ideally, we would see evidence that the systematic incorporation of TEB results into an antihypertensive treatment algorithm leads treating physicians to prescribe different classes of medications or more appropriate dosages of the same medications than they would otherwise have prescribed, and that patients whose treatment is changed by TEB results remain on the regimen and achieve better long term blood pressure control documented by repeated measurements over time. Unfortunately the data do not establish that the treating physicians actually adhered to the recommended treatment algorithm in the hemodynamic group.

It would be informative to know for all the study participants what specific drug regimen the physician prescribed without TEB results, and what different drug regimen the physician prescribed after knowing the TEB results. We would then be able to determine not only the frequency with which TEB results brought about treatment changes, but also what kinds of changes were made and the durability of those changes, i.e. did the patient stay on the TEB-indicated treatment and did the BP remain under long term control. Unfortunately the data presented in the CONTROL trial do not permit us to answer these questions affirmatively.

Had medication changes been reported along with the hemodynamic data that may have prompted them, it would be much easier to interpret the study results. For example, baseline use of medication is reported by drug type; e.g. ACEI (angiotensin converting enzyme inhibitor), ARB (angiotensin II receptor blocker), CCB (calcium channel blocker), and percentage of patients in each group using each type with a *p* value for the difference between groups. At the first post-washout visit patients in the hemodynamic arm were more likely to be prescribed an ACEI, ARB or CCB (92.5% versus 80.0%; $p < 0.05$). Over the course of the study, patients in the hemodynamic arm were more likely to be prescribed an ACEI, ARB, or CCB when their SVRI was high, per the hemodynamic treatment strategy (78.3% versus 67.1%; $p < 0.05$), but no information is provided as to what patients' responses were to institution or change of dose of any of these medications. Moreover, there were no reported differences in the use of 2 other treatments encouraged by the hemodynamic treatment strategy: β blocker use based on high CI (cardiac index), or diuretic use when TFC (thoracic fluid content) did not decrease in response to diuretic initiation or dosage increase.

In attempting to analyze medication changes occurring during the study, which might have been attributed to hemodynamic data, the only change reported as statistically significant ($p < 0.05$) was the increase in the use of ARBs from baseline to final visit, from 14 to 29 in SC group and from 20 to 32 in HC group. The hemodynamic measure that should have led to this change would have been high SVRI. However, the magnitude of the SVRI is not reported, and it is unclear whether all patients getting a medication change responded with decreased BP and decreased SVRI, and whether the BP reduction was sustained or required additional dosing changes.

Differences in diuretic use are reported as non-significant, but information about diuretic use is reported differently from baseline to final. At baseline, 30 SC patients are reported to be using diuretics, but final medications are broken down into three types of diuretics (thiazide, loop and potassium sparing) and 39 SC patients are reported to be taking one of them. At baseline, 18 HC patients are reported to be on diuretics, but using the 3 types reported in final medications, 27 HC patients are receiving diuretics and the changes in total patients using diuretics at the conclusion of the study appear to be statistically significant in both groups.

A similar reporting change appears with CCB use. At baseline, 32 SC patients are reported to be receiving CCBs. Final medication data break CCBs into dihydropyridine and nondihydropyridine types and a total of 42 SC patients are reported to be using one or the other. For the HC group, at baseline, 27 are using CCBs, but final medications show 35 patients using one of the two types of CCBs. The differences in CCB use also appear significant.

Using the hemodynamic strategy as a guide, the change in CCBs should have resulted from high SVRI and the change in diuretic use from TFC measurement in the HC group. The authors note there was actually more improvement in TFC in the SC group, which they attribute to higher doses of thiazide diuretics, which did not lead to a greater decrease in BP. Again, in the absence of visit-to-visit hemodynamic or medication information, we cannot determine whether changes in BP were occurring in the HC group as predicted when following the hemodynamic strategy.

From the material noted above we cannot determine the answers to a number of additional points.

- How high did the SVRI have to be to prompt a medication change, and what was the absolute difference in the hemodynamic data between patients in the two arms?
- Did the physicians using hemodynamic data respond with medication changes to even very small changes from visit-to-visit, and did BP respond to medication changes by the next visit?
- Did visit-to-visit hemodynamic data differ in the two groups and could those differences be attributed to medication choices?

Even though the standard care group's data were not used in treatment planning, they were collected and could have been analyzed to determine whether they would have impacted treatment decisions had they been used. TEB provides an array of hemodynamic information, but even though physicians had been educated on its use in treating hypertension, it appears that data such as CI and TFC were ignored in the hemodynamic group. This creates uncertainty about the general clinical utility of data derived through TEB.

The authors state that their "results demonstrate the ICG-guided antihypertensive treatment was more effective in reducing BP than standard therapy and empiric selection of antihypertensive medications," but have failed to present data sufficient to support this conclusion. The lack of information about the numbers of physicians in the HC group actually using hemodynamic data is a critical omission. Further, the absence of change in cardiac index and thoracic fluid content in the HC group suggests that the HC treatment strategy was not actually used in a number of patients in the HC group or that it was not effective if used, since similar results were achieved without ICG data in the SC group. More patients in the HC group did achieve BP<140/90, but within the group we cannot determine how many achieved this goal without their physicians having made use of hemodynamic data.

Although not a primary endpoint, the authors did subgroup analysis to determine how many patients in each group achieved BP <130/85 and found that 55 patients in the HC group and 27 patients in the SC group reached this level of control. It is not clear how many of the 55 HC patients were actually treated using the suggested protocol and ICG-guided data. We do not know if there also were other improvements in hemodynamic parameters, such as CI and TFC, that may not have been apparent in the whole group.

Another major limitation of the study, which the authors concede and which is pointed out in Flack's accompanying editorial, is the short duration of the study. Hypertension is a life-long disease and generally progressive over time. Three months of BP control is insufficient to draw conclusions about long-term effectiveness of any treatment strategy.

Flack's editorial also raises the question of whether abnormal hemodynamic parameters noted in the course of treatment of hypertension need to be normalized and concludes that the question "cannot be answered until future studies link improvements in pressure-related clinical outcomes or, at the very least, in clinically relevant measures of target-organ damage, such as left ventricular mass and function and/or microalbuminuria, to normalization of hemodynamic parameters independent of BP normalization."

Flack's questions begin to get at an important issue that has not been addressed in the CONTROL study or in any other literature that we have been able to locate. How is TEB expected to be used clinically?

- When is TEB medically necessary? Should every newly diagnosed hypertensive patient have a TEB assessment or would it only be appropriate for patients undergoing treatment who fail to achieve a goal BP after some specified period of time?
- How long should one try to achieve that goal before using TEB?
- Is TEB expected to be routinely used with every medication change to determine if that change was appropriate, regardless of the blood pressure outcome?
- What is the evidence for routine use of TEB in hypertensive patients, particularly in the elderly? If physicians participating in a study of utility of hemodynamic data did not use it in study patients, what is the demonstrated or likely use of that data in other populations?

We have considered what kind of trial design could, if the results were positive, affirmatively answer the core question that we restate here.

Is the evidence sufficient to conclude that hemodynamic monitoring with thoracic electric bioimpedance (TEB), when used by the treating physician to guide management of the patient's medical problem, improves health outcomes in Medicare beneficiaries with hypertension who are on one or more antihypertensive drugs and who are not at goal blood pressure?

Such a trial would collect data on the physician's planned management before and after TEB results at each visit and to see if the management plan was changed after the TEB results were known. The hemodynamic rationale for any change would be noted. The specific nature of the change would be documented, or the rationale for no change would be provided. Subject adherence to the management would be rigorously assessed, and we would be able to determine if the TEB-indicated regimen was maintained or whether the subject ultimately ended up on a different regimen. Whether the TEB-indicated regimen had the expected effect on the hemodynamic parameter and if that was associated with better blood pressure control over time should be assessed. Do hemodynamic parameters remain abnormal in patients who achieved normal blood pressure measurements? Are all hemodynamic abnormalities of equal relevance to normalization of blood pressure?

In light of the outstanding concerns noted above, we believe that a trial purporting to demonstrate significant health benefits in Medicare beneficiaries resulting from the use of TEB should include and report the following characteristics.

1. Enrolled subjects should represent the age and disease characteristics of Medicare beneficiaries who have hypertension, including disease severity and comorbidities.
2. Information as to what specific treatments including efforts at life style modifications and how long subjects had been under treatment for hypertension prior to their beginning the trial should be collected to assess the need for use of TEB. Hypertension that has not received standard care would not seem to require TEB and with adherence to a good regimen goal BP should be achieved.

3. Subjects should be followed for a minimum of 6 months, preferably 12 months, to measure the durability of their blood pressure control, the stability of the prescribed regimen, and their adherence to prescribed antihypertensive regimens.
4. Subject adherence to the prescribed medication regimen should be objectively measured rather than relying of self-reported recall of adherence. The reasons for nonadherence, e.g. intolerance, adverse event, new contraindication, excessive complexity of the regimen, etc. should be reported
5. Antihypertensive medication use should be classified and described consistently throughout the study. For example, if CCBs are broken down by subclass for the results, subclass level information should be reported for the baseline as well.
6. Physician adherence to the hemodynamic protocol should be documented, i.e. how often did physician prescriptions for antihypertensive therapy follow the TEB-guided protocol?
7. It could be helpful to note if the physician's prescription after knowing the TEB result varies with the physician recommendation before the TEB result, and if so the nature of the variations.
8. Correlation, if any, between the normalization of hemodynamic parameters and blood pressure control should be reported.
9. Over the course of the study, it would be informative to report whether TEB results obtained at baseline are sufficient to guide chronic treatment. Are the physicians' treatment decisions largely determined at the initial evaluation, i.e. can the patient can be classified as likely to benefit from a particular regimen, including sequential medication changes, based on an initial hemodynamic profile? Or will the treatment regimen be significantly revised based on later TEB results? In other words, is there a benefit to repeated measurement, possibly continuing even after the subject has achieved goal blood pressure?
10. Blood pressure measurement technique and frequency should be standardized among the study centers and from visit to visit for individual subjects. Inter-rater reliability should be addressed.
11. TEB measurement technique and frequency should be similarly standardized and reported.
12. Followup frequency should be standardized and reported. For example, will the timing of the subjects' return to the physician be predetermined by the blood pressure, the medication regimen, or other factors? If the subject returns before the scheduled visit, e.g. for a respiratory infection, will TEB be performed, will blood pressure be recorded, and will antihypertensive regimens be adjusted?
13. Subject attrition should be reported for each study group, along with reasons for attrition.
14. Intention to treat analysis is preferable.
15. A description of antihypertensive treatment-related adverse events experienced by the subjects, e.g. hypotension, cardiac dysrhythmia, electrolyte and acid-base abnormalities, cognitive dysfunction, etc. would provide useful information on whether TEB-guided management can affect the frequency or severity of such events.

As discussed in the Evidence and Public Comment sections above, CardioDynamics submitted additional information about the CONTROL trial that had not been included in the published article, in response to some of the questions CMS had noted in the proposed decision memorandum. We reviewed that additional material and found informative but not persuasive on the request.

The absence of a direct link from the intervention to the reported outcome is at the core of our reservations about the CONTROL trial. We recognize that the subjects in the hemodynamic monitoring arm generally achieved tighter short term blood pressure control than the subjects in the standard care arm. As we noted in the proposed decision memorandum and above, data are lacking that treating physicians, armed with TEB test results, made specific changes to the treatment that would otherwise have been administered.

42 CFR 410.32 states in part, "…diagnostic tests must be ordered by the physician who is treating the beneficiary, that is, the physician who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem…" We believe that this requires CMS to determine, in the case of this reconsideration of the NCD, that the test results are being used in the manner described in the regulation. However, we have been unable to determine, because of the trial methodology and the reported data, that the treating physicians actually used the results of TEB testing to achieve the reported outcome.

We believe that many patients in the CONTROL study were undertreated prior to entrance in the study in that, failing to reach goal BP with life style changes, the first drug prescribed for treatment of hypertension is generally a diuretic. A large percentage of both groups (42% of standard care group and 45% of hemodynamic care group) were on only one antihypertensive medication at baseline. Additional information noted that on average patients were receiving 1.7 antihypertensive medications at baseline. At baseline 31.6% of SC and 26.1% of HD arm subjects were taking diuretics of some sort (loop, potassium-sparing, or thiazide). The requestor's subsequent communication that the average time from study participant's original diagnosis to trial entry was 6.9±7.5 years does not speak highly of the adequacy of prior treatment. We would have expected most patients in community practice to be receiving a diuretic as part of any antihypertensive drug regimen unless there was a specific contraindication, especially if their blood pressure had remained uncontrolled for almost 7 years. Thus it appears that the lack of blood pressure control at baseline can be more readily attributed to inadequate attention to current treatment guidelines rather than to any inherent complexity of the patients' conditions or need for additional data to guide treatment. Since the goal of hypertension treatment is to normalize blood pressure and prevent end-organ damage, not to specifically normalize hemodynamic parameters, we are puzzled why these patients' abnormal blood pressures were not treated more aggressively in the first place.

Another issue that must be addressed because of the manufacturer's revised request is the potential for improper or ineffective use of TEB. We are concerned that only one professional society is endorsing use of TEB and that no society has proposed guidelines for appropriate use of this test. There appears to be no consensus among users offering comments as to the frequency of use or, clinical indicators for need of TEB testing. The requestor's proposed conditions, frequency limitation and noncoverage proposals appear to be an arbitrary attempt to impose restraints that might make the test more acceptable for third-party coverage. Neither the Mayo study nor CONTROL employed such limits nor have we been able to locate any data, which would support these proposals. But comments do indicate a need for guidance as to when TEB would be reasonable and necessary. A small number of commenters point to TEB as a way to supplement practitioner income and that cannot be a reason to provide Medicare reimbursement. We urge the requestor and others wishing to expand coverage to develop reasonable guidelines for the use of TEB based on sound principles of clinical judgment and clinical evidence of the effectiveness. Such guidelines would ideally be endorsed by societies and other major groups representing the practitioners using TEB.

The data presented in the CONTROL study are insufficient to establish the clinical benefit of hemodynamic monitoring with TEB as a means of achieving better blood pressure control in Medicare patients under treatment for hypertension who do not have drug resistant hypertension as defined in the current NCD. Thus we are unable to conclude that the use of TEB leads to improved health outcomes in Medicare beneficiaries who do not meet the criteria in Section 20.16 of the NCD Manual

IX. Conclusion

CMS was asked to make a National Coverage Determination (NCD) that would expand Medicare coverage to include Transthoracic Electrical Bioimpedance (TEB) for the management of drug resistant hypertension and additional types of hypertension. Our existing policy permits Medicare contractors to determine whether or not TEB is reasonable and necessary under § 1862(a)(1)(A) for management of drug resistant hypertension. 20.16(A)(2) of the Medicare National Coverage Determination Manual. After considering the additional evidence, we have determined that the evidence does not warrant expanded coverage at this time. Still, we will retain our policy permitting Medicare contractors to make a reasonable and necessary determination under § 1862(a)(1)(A) for the use of TEB in the management of drug resistant hypertension in beneficiaries.

APPENDIX A

General Methodological Principles of Study Design

(Section VI of the Decision Memorandum)

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.

Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.

Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.

Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.

Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).

Co-interventions or provision of care apart from the intervention under evaluation (performance bias).

Differential assessment of outcome (detection bias).

Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

Randomized controlled trials
Non-randomized controlled trials
Prospective cohort studies
Retrospective case control studies
Cross-sectional studies
Surveillance studies (e.g., using registries or surveys)
Consecutive case series
Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

APPENDIX B

American College of Cardiology Position Statements [PDF, 169KB]

International Society on Hypertension in Blacks [PDF, 224KB]

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